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(52) UK CL (Edition M)
C2C CAA CWK C1450 C215 C22Y C220 C246 C25Y C250 C252 C28X C29X C29Y C31Y C311 C36Y C360 C363 C623 C652 C697 C770 C778 C80Y C802
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(56) Documents Cited
GB 2099818 A

(58) Field of Search
UK CL (Edition L) C2C CWK
INT CL[5] C07D
ONLINE DATABASES: CAS ONLINE

(54) Crystalline monohydrate of 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol

(57) The monohydrate of 2-(2, 4-difluorophenyl)-1, 3-bis(1H-1, 2, 4-triazol-1-yl)propan-2-ol is useful for pharmaceutical formulation as an antifungal agent. It is less bitter than the non-hydrated compound and is stable under normal processing conditions.

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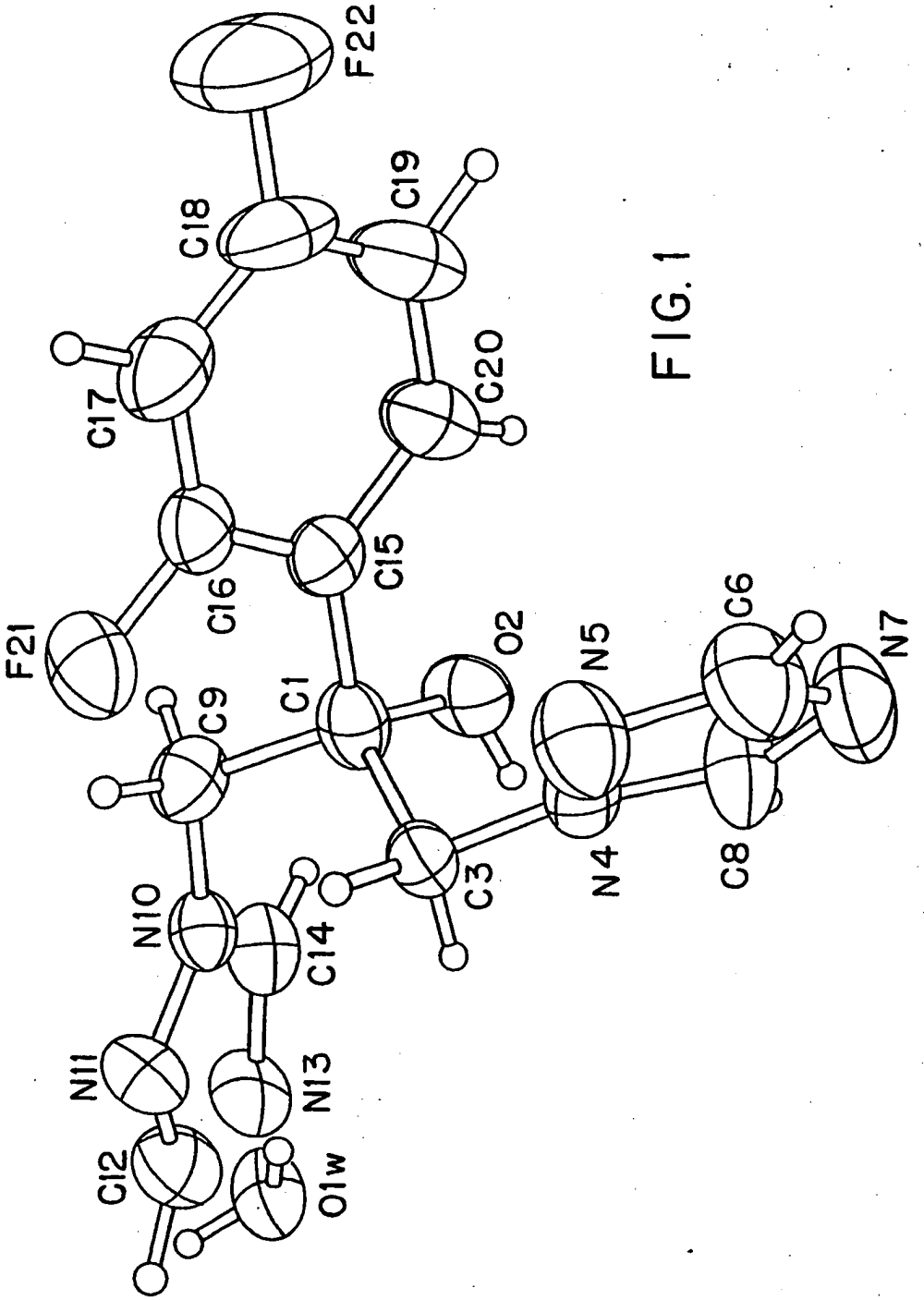
F22
C18
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C14
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N4
C8
N11
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C12
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FIG. 1

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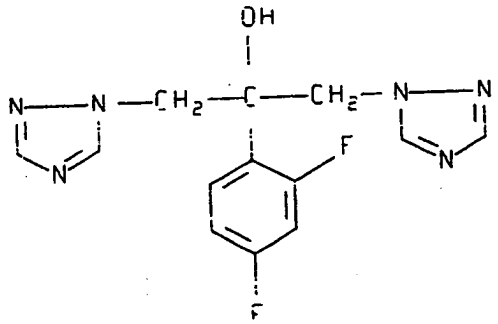
CRYSTALLINE MONOHYDRATE OF 2-(2,4-DIFLUOROPHENYL)-1,3-BIS(1H-1,2,4-TRIAZOL-1-YL)PROPAN-2-OL

Background of the Invention

The present invention is directed to a novel crystalline monohydrate of 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol having advantageous properties for pharmaceutical formulation as an antifungal agent, a pharmaceutical composition containing said monohydrate and a method of treatment comprising administering said monohydrate.

Richardson, U.S. Patent No. 4,404,216, which is incorporated herein by reference, has disclosed said 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol, of the formula



I

or a pharmaceutically acceptable salt as an especially preferred compound for use as an antifungal agent.

The compound of formula I is known for its bitter taste and previous taste masking techniques using various sweeteners, amino acids, acids, flavors and adsorbents have been unsuccessful in masking said bitterness.

Summary of the Invention

The present invention comprises the monohydrate form of 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol (hereafter "the monohydrate") which possesses valuable and unobvious properties. Thus, this monohydrate is less bitter, and stable under normal processing conditions for formulation into chewable, lozenge, and fast-dissolving conventional dosage forms such as capsules and tablets.

Brief Description of the Drawings

Fig. 1 is the structure of the monohydrate based on single crystal X-ray crystallography, showing that the water molecule of the monohydrate, designated as O1w, is adjacent to one of the triazole moieties of the compound of formula I.

Detailed Description of the Invention

The compound of the present invention is readily prepared by dissolving 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol compound in hot water and cooling the resulting solution to room temperature thus precipitating the monohydrate in the form of acicular shaped crystals. In contrast to the anhydrous form of the compound of formula I, the monohydrate is less bitter.

The present monohydrate may be administered as an antifungal agent as described in above-mentioned U.S. Patent 4,404,216. Administration to a human subject may be alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents in a pharmaceutical composition, in accordance with standard pharmaceutical practice. The monohydrate may be administered orally or parenterally including intravenously or intramuscularly. Suitable pharmaceutical carriers include solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions are then readily administered in a variety of dosage forms, such as tablets, powders, lozenges, syrups, and injectable solutions. These pharmaceutical compositions, if desired, may contain additional ingredients such as flavorings, binders and excipients. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When an aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solution of the monohydrate in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The effective dosage for the monohydrate depends on the intended route of administration and other factors such as age and weight of the subject, as generally known. For oral administration to human patients, the effective dosage for the monohydrate will be 0.1 to 5.0 mg/kg per day. Thus, tablets can generally be expected to contain anywhere from approximately 5.0 to 500 mg of the monohydrate.

EXAMPLE 1

2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol monohydrate

Anhydrous 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol (10 grams) was added to de-ionized water (100 ml) while stirring with a magnetic stirring bar. The water was heated to 95°C to completely dissolve the 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol. Stirring was continued for 5 minutes. The solution was then allowed to cool to room temperature (approximately 25°C) without stirring. Upon standing, precipitates of 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol monohydrate were formed as acicular shaped crystals. The solution was allowed to stand for one additional hour at room temperature. The 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol monohydrate crystals were filtered on a fritted glass filter (10-20 micron) with room air pulled through the filter by vacuum for 24 hours, mp 138°C. The water content in the 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol monohydrate was found to be 5.60% by the Mitsubishi Moisture Meter. This water content corresponded approximately to one water molecule per 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol molecule. The water content of the anhydrous 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol, used as the starting material, was found to be 0.1%. Anal. Calc. for $C_{13}H_{14}N_6O_2F_2$: C, 48.15; H, 4.35; N, 25.90. Found: C, 48.48; H, 4.09; N, 25.98. Mp 138°C.

EXAMPLE 2

2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol monohydrate

Anhydrous 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol (100 grams) was added slowly to deionized water (1300 ml) upon stirring with a magnetic stirring bar to form a slurry. Stirring of the slurry at room temperature was continued for one hour. The slurry was then filtered on a fritted glass filter (10-20 micron) under vacuum. The 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol monohydrate crystals were dried on the fritted glass filter (10-20 micron) with room air pulled through the filter by vacuum for 24 hours, mp 138°C. The water content in the 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol monohydrate was found to be 5.76% by the Karl Fischer Titration method. This water content corresponded approximately to one water molecule per 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol molecule. The water content in the anhydrous 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol was found to be 0.1%. Anal. Calc. for $C_{13}H_{14}N_6O_2F_2$: C, 48.15; H, 4.35; N, 25.90. Found: C, 47.90; H, 4.17; N, 25.59. The following tables illustrate the spectrometric differences between the anhydrous and the monohydrate compounds:

Table 1: Power X-ray diffraction study of the monohydrate.

No.	2Theta	d	Rel I (%)	Max I	Integ I	Width	Type
Range #1							
1	5.042	17.5267	4.5	158.	67.21	0.155	KA
2	8.001	11.0502	2.6	91.	38.72	0.176	KA
3	8.441	10.4752	1.1	37.	15.81	0.227	KA
4	9.242	9.5690	11.8	411.	174.82	0.200	KA
5	10.080	8.7753	100.0	3470.	1477.15	0.200	KA
6	12.200	7.2548	1.8	63.	26.68	0.166	KA
7	12.724	6.9571	2.1	73.	30.92	0.163	KA
8	13.860	6.4730	10.5	363.	154.38	0.187	KA
9	15.122	5.8589	12.7	440.	187.30	0.202	KA
10	15.441	5.7385	9.2	321.	136.46	0.169	KA
11	16.240	5.4580	32.9	1140.	485.31	0.205	KA
12	16.639	5.3280	90.2	3131.	1332.98	0.243	KA

No.	2Theta	d	Rel I (%)	Max I	Integ I	Width	Type
Range #1							
13	17.721	5.0050	2.8	96.	41.01	0.255	KA
14	18.368	4.8302	0.9	31.	13.13	0.140	KA
15	18.920	4.6905	3.5	123.	52.21	0.187	KA
16	20.160	4.4047	58.9	2045.	870.66	0.244	KA
17	20.561	4.3197	14.4	500.	213.03	0.203	KA
18	21.199	4.1911	18.1	626.	266.64	0.234	KA
19	22.080	4.0258	5.7	199.	84.64	0.273	KA
20	22.961	3.8733	1.3	45.	19.31	0.110	KA
21	23.201	3.8338	1.1	39.	16.42	0.150	KA
22	23.681	3.7571	2.4	83.	35.37	0.191	KA
23	24.032	3.7031	8.8	306.	130.19	0.145	KA
24	25.083	3.5502	6.6	229.	97.59	0.281	KA
25	25.721	3.4636	17.7	616.	262.15	0.246	KA
26	26.401	3.3759	2.2	77.	32.91	0.118	KA
27	27.204	3.2781	4.2	147.	62.55	0.126	KA
28	27.520	3.2411	9.6	332.	141.19	0.206	KA
29	28.043	3.1819	2.1	73.	31.13	0.100	KA
30	28.398	3.1429	1.9	65.	27.51	0.179	KA
31	28.879	3.0916	2.6	91.	38.59	0.141	KA
32	29.359	3.0422	16.4	568.	241.93	0.274	KA
33	30.161	2.9631	2.3	81.	34.64	0.129	KA
34	30.399	2.9404	4.0	139.	59.09	0.245	KA
35	31.202	2.8665	1.3	45.	19.12	0.152	KA
36	31.518	2.8385	0.8	29.	12.42	0.134	KA
37	32.522	2.7532	2.0	69.	29.55	0.169	KA
38	34.878	2.5724	1.9	65.	27.87	0.299	KA
39	36.120	2.4867	2.4	84.	35.70	0.190	KA
40	37.680	2.3873	0.5	19.	8.07	0.212	KA
41	39.205	2.2979	0.6	20.	8.33	0.129	KA

Table 2: Power X-ray diffraction study of the anhydrous compound.

No.	2Theta	d	Rel 1 (%)	Max 1	Integ 1	Width	Type
Range #1							
1	4.717	18.7534	0.3	32.	13.77	0.150	KA
2	7.407	11.9430	3.3	310.	132.04	0.194	KA
3	11.640	7.6025	8.1	771.	328.32	0.191	KA
4	12.124	7.3001	0.7	65.	27.64	0.157	KA
5	13.364	6.6254	1.3	120.	51.02	0.180	KA
6	14.279	6.2028	2.9	274.	116.76	0.167	KA
7	14.802	5.9848	70.8	6714.	2858.69	0.190	KA
8	15.761	5.6227	15.5	1468.	624.79	0.187	KA
9	17.323	5.1191	33.1	3136	1335.18	0.165	KA
10	18.200	4.8744	1.9	176.	74.75	0.115	KA
11	18.518	4.7914	15.3	1455.	619.65	0.165	KA
12	19.560	4.5384	16.8	1591.	677.46	0.172	KA
13	19.719	4.5022	16.0	1516.	645.38	0.217	KA
14	20.083	4.4214	8.1	767.	326.51	0.156	KA
15	22.239	3.9974	3.7	352.	149.70	0.198	KA
16	23.920	3.7201	3.7	356.	151.43	0.161	KA
17	24.439	3.6423	100.0	9487.	4039.22	0.192	KA
18	24.960	3.5674	5.3	504.	214.78	0.202	KA
19	25.362	3.5118	2.0	185.	78.97	0.146	KA
20	25.762	3.4582	2.3	213.	90.89	0.161	KA
21	26.240	3.3963	4.5	432.	183.71	0.197	KA
22	26.879	3.3169	13.9	1316.	560.14	0.225	KA
23	27.440	3.2504	1.3	127.	53.87	0.182	KA
24	28.724	3.1080	0.7	65.	27.69	0.150	KA
25	29.241	3.0542	14.9	1415.	602.46	0.190	KA
26	29.523	3.0256	2.6	246.	104.77	0.114	KA
27	30.320	2.9770	0.4	37.	15.82	0.105	KA
28	30.718	2.9106	0.8	78.	33.13	0.114	KA

No.	2Theta	d	Rel I (%)	Max I	Integ I	Width	Type
Range #1							
29	31.000	2.8848	4.1	393.	167.41	0.166	KA
30	31.320	2.8560	22.3	2115.	900.43	0.202	KA
31	31.517	2.8386	9.0	850.	361.88	0.087	KA
32	31.877	2.8074	1.2	112.	47.86	0.093	KA
33	32.161	2.7832	0.9	88.	37.67	0.190	KA
34	32.962	2.7174	1.2	110.	46.95	0.195	KA
35	33.160	2.7016	0.9	83.	35.16	0.130	KA
36	34.564	2.5950	2.1	201.	85.62	0.313	KA
37	35.082	2.5579	1.0	91.	38.64	0.190	KA
38	35.414	2.5347	.04	38.	16.07	0.150	KA
39	36.481	2.4630	.06	58.	24.57	0.289	KA
40	36.880	2.4372	1.8	174.	74.26	0.232	KA
41	37.553	2.3951	0.3	25.	10.72	0.128	KA
42	38.763	2.3231	0.7	68.	28.98	0.186	KA
43	39.684	2.2712	0.6	58.	24.60	0.154	KA

Table 3: Infrared study of the monohydrate.

X = Wave Number (cm^{-1})
Y = % Transmittance

Minima List:

X=	401.01	Y=	74.671
X=	412.24	Y=	65.302
X=	423.41	Y=	69.309
X=	472.19	Y=	61.388
X=	514.09	Y=	41.887
X=	524.54	Y=	24.319
X=	575.83	Y=	35.241
X=	585.79	Y=	49.565
X=	616.08	Y=	34.126

X = Wave Number (cm^{-1})
Y = % Transmittance

Minima List:

5	X=	652.56	Y=	24.234
	X=	674.27	Y=	21.966
	X=	691.16	Y=	45.287
	X=	710.76	Y=	45.072
	X=	733.47	Y=	44.637
10	X=	768.57	Y=	40.909
	X=	803.16	Y=	38.163
	X=	830.79	Y=	43.960
	X=	846.54	Y=	24.417
	X=	861.01	Y=	39.058
15	X=	869.03	Y=	35.567
	X=	888.11	Y=	40.091
	X=	911.51	Y=	40.687
	X=	960.59	Y=	30.637
	X=	967.40	Y=	26.596
20	X=	999.88	Y=	53.728
	X=	1011.6	Y=	35.138
	X=	1026.0	Y=	46.938
	X=	1075.3	Y=	29.632
	X=	1090.5	Y=	34.521
25	X=	1115.8	Y=	24.541
	X=	1137.8	Y=	19.882
	X=	1158.7	Y=	58.609
	X=	1178.1	Y=	68.849
	X=	1203.7	Y=	33.344
30	X=	1233.2	Y=	56.861
	X=	1254.2	Y=	36.911
	X=	1272.4	Y=	21.017
	X=	1300.6	Y=	43.687

X = Wave Number (cm^{-1})
Y = % Transmittance

Minima List:

	X=	1317.4	Y=	50.529
	X=	1343.2	Y=	46.875
	X=	1353.1	Y=	46.096
	X=	1367.3	Y=	45.838
	X=	1418.1	Y=	29.272
	X=	1452.1	Y=	40.817
	X=	1463.6	Y=	45.921
	X=	1480.2	Y=	51.373
	X=	1502.4	Y=	20.792
	X=	1514.5	Y=	25.369
	X=	1520.2	Y=	24.828
	X=	1598.2	Y=	36.532
	X=	1619.8	Y=	31.939
	X=	1690.1	Y=	71.970
	X=	1733.1	Y=	66.893
	X=	1755.8	Y=	71.135
	X=	1774.0	Y=	66.912
	X=	1916.3	Y=	73.697

Table 4: Infrared study of the anhydrous compound.

X = Wave Number (cm^{-1})
Y = % Transmittance

Minima List:

	X=	411.35	Y=	51.675
	X=	464.40	Y=	49.164
	X=	484.88	Y=	66.633
	X=	515.93	Y=	33.593
	X=	523.91	Y=	24.889
	X=	568.75	Y=	29.813

X = Wave Number (cm^{-1})
Y = % Transmittance

Minima List:

5	X=	586.90	Y=	43.586
	X=	609.08	Y=	28.770
	X=	646.70	Y=	31.081
	X=	658.14	Y=	27.625
	X=	680.30	Y=	21.359
10	X=	701.67	Y=	36.961
	X=	739.01	Y=	38.490
	X=	761.24	Y=	34.696
	X=	793.82	Y=	41.455
	X=	817.56	Y=	35.233
15	X=	851.26	Y=	21.403
	X=	884.99	Y=	26.713
	X=	896.02	Y=	36.000
	X=	909.33	Y=	30.190
	X=	928.60	Y=	50.259
20	X=	966.55	Y=	21.207
	X=	1001.9	Y=	42.482
	X=	1011.5	Y=	32.103
	X=	1017.5	Y=	30.487
	X=	1078.8	Y=	24.712
25	X=	1085.2	Y=	24.896
	X=	1104.4	Y=	20.493
	X=	1144.5	Y=	19.156
	X=	1211.0	Y=	29.764
	X=	1219.6	Y=	31.157
30	X=	1235.5	Y=	49.883
	X=	1260.5	Y=	32.430
	X=	1279.2	Y=	17.401
	X=	1293.8	Y=	33.097

X = Wave Number (cm^{-1})
Y = % Transmittance

Minima List:

5	X=	1316.9	Y=	43.567
	X=	1343.5	Y=	32.684
	X=	1386.5	Y=	28.788
	X=	1420.2	Y=	22.072
	X=	1433.2	Y=	32.823
10	X=	1449.4	Y=	37.313
	X=	1507.0	Y=	16.764
	X=	1515.5	Y=	21.299
	X=	1559.9	Y=	60.459
	X=	1601.2	Y=	36.711
15	X=	1619.6	Y=	22.969
	X=	1664.2	Y=	70.951
	X=	1698.5	Y=	72.428
	X=	1766.0	Y=	60.178
	X=	1817.6	Y=	79.273
20	X=	1844.2	Y=	68.662
	X=	1899.1	Y=	71.926

CLAIMS

1. The monohydrate of 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol.

2. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antifungal amount of a compound as claimed in claim 1.

3. A method of treating fungal infections in a warm blooded animal, which comprises administering to said animal an antifungal amount of a compound as claimed in claim 1.

Patents Act 1977 -13-
Examiner's report to the Comptroller under Section 17 (The Search Report)

Application number
GB 9318592.4

Relevant Technical fields

(i) UK Cl (Edition L) C2C CWK

(ii) Int Cl (Edition 5) C07D

Search Examiner
P N DAVEY

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASES: CAS ONLINE

Date of Search
4 OCTOBER 1993

Documents considered relevant following a search in respect of claims 1-3

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
A	GB 2099818 A (PFIZER) See eg Claim 1	1-3

Category	Identity of document and relevant passages — 14 —	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

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